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Review article

Neurofunctional abnormalities in antisocial spectrum: A meta-analysis of fMRI studies on Five distinct neurocognitive research domains

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ABSTRACT

Past functional magnetic resonance imaging on antisocial subjects have shown important inconsistencies and methodological problems (e.g. heterogeneity in fMRI tasks domain, small sample sizes, analyses on regions-of-interest). We aimed to conduct a meta-analysis of whole-brain fMRI studies on antisocial individuals based on distinct neurocognitive domains. A voxel-based meta-analysis via permutation of subject images (SDM-PSI) was performed on studies using fMRI tasks in the domains of acute threat response, cognitive control, social cognition, punishment and reward processing. Overall, 83 studies were retrieved. Using a liberal statistical threshold, several key regions were identified in the meta-analysis, principally during acute threat response, social cognition and cognitive control tasks. Additionally, we observed that the right amygdala was negatively associated with both callous-unemotional traits and severity of antisocial behaviors, in meta-analyses on region-of-interest and on dimensional studies, respectively. The findings show that the most prominent functional brain deficits arise during acute threat response, social cognitions and cognitive control neurocognitive domains. These results provide substantial insights for our understanding of aberrant neural processing across specific contexts.

1. Introduction

Conduct problems (CP) and its adult form, adult antisocial behaviors are usually defined as behaviors that frequently violate the rights of others (i.e. aggressive and rule-breaking behaviors). Developmental research suggests approximately 5% of children would display severe and persistent CP, thus meeting the criteria for conduct disorder (CD) (Bevilacqua et al., 2018). The presence of CP at an early age has been associated with poor adult outcomes such as antisocial behaviors, high rates of criminality, incarcerations, substance misuse and poor general health (Moffitt, 2018). By studying antisocial problems as a dimensional construct (i.e. problems to antisocial personality disorder (CP/ASPD)), evidence from literature reviews suggests that individuals on the antisocial spectrum show several deficits in brain functioning across various distinct neurocognitive domains (Blair et al., 2018; Blair, 2010; Byrd et al., 2014; Crowe and Blair, 2008; Del Casale et al., 2015; Glenn and Raine, 2008; Herpers et al., 2014; Seara-Cardoso and Viding, 2015; Wahlund and Kristiansson, 2009). Nevertheless, consensual evidence about the nature and severity of neural dysfunctions during cognitive and emotional tasks are still lacking. It is thus crucial to better understand the neurobiological impairments in antisocial subjects, across different contexts (i.e. specific neurocognitive research domains), in order to facilitate early prevention research.

1.1. Acute threat response

The acute threat response system or the defensive survival circuit involves physiological reactions (i.e. autonomic nervous and endocrine

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systems) and adaptive behaviors (i.e. fight, flight or freeze response) when facing a threatening stimulus (LeDoux, 2015). Concerning CP/ASPD subjects, it has been proposed that brain regions involved in response to threat (i.e. amygdala, ventromedial prefrontal cortex (PFC), dorsal anterior cingulate cortex, insular cortex, hypothalamus and peri-aqueductal gray) may be largely implicated in aggression (Blair et al., 2018; Blair, 2016; Crowe and Blair, 2008). A recent literature review suggests that CP/ASPD individuals show reduced Hypothalamic-Pituitary-Adrenal axis function in response to threat compared to healthy controls (HC) (Fairchild et al., 2018). Furthermore, a meta-analysis on fMRI studies of CP/ASPD subjects found significant underactivation in dorsolateral PFC and temporal pole during emotion processing (Alegria et al., 2016). Additionally, a meta-analysis that focused specifically on psychopathic individuals but pooled studies using fMRI tasks belonging to heterogeneous neurocognitive domains, showed that psychopathic subjects exhibited reduced activation in the right laterobasal amygdala, bilateral lateral PFC and dorsomedial PFC and an increased activation in bilateral fronto-insular cortex compared to HC (Poeppl et al., 2019). Thus, it was hypothesized that callous-unemotional traits (CU) may moderate neural functioning in response to acute threat in antisocial individuals (i.e. hypo- and hyper-reactivity to threat may be associated with CP/ASPD with and without CU traits, respectively, see Blair et al., 2014; Hyde et al., 2013; Viding et al., 2012a). Evidence for this assertion remains however limited.

1.2. Cognitive control

Cognitive control refers to the neurocognitive domain of executive functions that require the overriding of interfering responses (i.e. motor and interference inhibition, cognitive flexibility, and performance monitoring) (Miller and Cohen, 2001). Neuropsychological studies show that CP/ASPD subjects exhibit poorer executive functioning, particularly in motor and interference inhibition and response selection tasks compared to HC (Hobson et al., 2011; Morgan and Lilienfeld, 2000; Ogilvie et al., 2011; Séguin et al., 2007). Literature reviews on fMRI studies of cognitive control tasks show that these deficits in CP/ASPD subjects are underpinned by decreased activation in the inferior frontal gyrus, insula, temporal lobe and supplementary motor area (Blair et al., 2018; Matthys et al., 2013; Noordermeer et al., 2016), and to a lesser extent, the precuneus and cingulate cortex (i.e. from anterior to posterior) (Noordermeer et al., 2016). Furthermore, Alegria et al.'s (2016) meta-analysis on cool executive function tasks revealed decreased activations in the right superior and middle temporal gyrus, posterior insula and putamen. However, their meta-analysis was underpowered ($k = 8$); more evidence is needed to support such neural impairments during cognitive control tasks.

1.3. Social cognitions

In the previous decades, researchers have observed important deficits in social cognition (i.e. lack of empathy and remorse) in subjects on the CP/ASPD spectrum. These researchers found a significant deficiency in recognizing/experiencing others' pain/distress (i.e. cognitive/affective empathy) (Blair et al., 2014; Dawel et al., 2012; Marsh and Blair, 2008; Martin-Key et al., 2018). It was proposed that these deficits may be principally exacerbated by the co-occurrence of psychopathic traits, particularly the CU dimension of psychopathy (Blair, 2013; Blair et al., 2014). However, although an earlier meta-analysis on facial affect recognition found robust evidence between deficits in recognizing fearful expressions in individuals with antisocial behaviors, psychopathy did not moderate the results (Marsh and Blair, 2008). Furthermore, while some found no significant differences between individuals with and without CU traits in empathic accuracy, emotion recognition and affective empathy (Martin-Key et al., 2017), others observed that emotion recognition problems were associated with CU traits (Dawel et al., 2012). That said, deficits in social cognitions in CP/ASPD individuals may therefore arise from reduced activations in the amygdala, anterior insula, cingulate cortex and temporo-parietal junction (Blair et al., 2018). Though, since these preliminary findings were based on a limited number of studies, a meta-analysis is necessary to examine these earlier indications of neural dysfunctions during social cognitions tasks.

1.4. Reinforcement learning

Finally, punishment and reward processing are key components in human motivation. An insensitivity to punishment (e.g. incapacity to learn from aversive stimuli) has been associated with antisocial problems, while hypersensitivity to reward-seeking has been associated with predatory/instrumental subtype of aggression (Xu et al., 2009). Most CP/ASPD individuals appear insensitive to punishment cues, whereas some display a high propensity for reward-seeking (Byrd et al., 2014 for a review of behavioral studies). Both components are related to a similar brain network (i.e. ventral striatum, amygdala, anterior insula, medial orbitofrontal cortex, ventromedial PFC and ventrolateral PFC, anterior cingulate cortex, however the medial orbitofrontal cortex seems to be more often elicited during reward processing, while punishment processing may recruit the middle cingulate cortex (Dugré et al., 2018; Knutson and Greer, 2008; Liu et al., 2011; Oldham et al., 2018). Although literature reviews suggest alterations in the striatum and ventromedial PFC in response to reward and punishment in CP/ASPD individuals (Blair et al., 2018; Byrd et al., 2014; Matthys et al., 2013), results suggest discrepancies on the directionality of such activations (i.e. hyper- and hypo-activations) (Blair et al., 2018; Murray et al., 2017).

1.5. Limitations of past neuroimaging studies on individuals with CP/ASPD

Our understanding of neural processing in CP/ASPD individuals is limited in current literature due to several weaknesses. In fact, discrepancies in fMRI results may derive from small sample sizes, comorbid CU traits, distinct methodology (i.e. whole-brain [WB], region-of-interest [ROI] or regression analyses) as well as the use of different statistical thresholds. For instance, literature reviews of fMRI studies (R. Blair et al., 2018; R. J. R. Blair, 2010; Byrd et al., 2014; Crowe and Blair, 2008; Del Casale et al., 2015; Glenn and Raine, 2008; Herpers et al., 2014; Seara-Cardoso and Viding, 2015; Wahlund and Kristiansson, 2009) report some results from brain regions that were statistically significant in ROI analyses (e.g. amygdala/PFC), but not in WB analyses. This is critical as ROI analyses substantially reduce the severity of correction for multiple tests (i.e. correcting for a few regions instead of the whole brain) and limit the anatomical inference to selected ROIs (Poldrack, 2007). Therefore, including ROI results in the interpretation of neural functioning of CP/ASPD subjects across the whole brain may increase the rate of false positives and type 1 errors. However, it remains crucial to perform a ROI-based meta-analysis in order to better understand the relationship between amygdala activity and the antisocial spectrum.

Additionally, previous meta-analyses did not take into consideration the heterogeneity of fMRI tasks used in studies included, even though different neurocognitive domains are known to be associated with distinct underlying brain networks. For example, while some authors performed a meta-analysis independently of task domains (Poeppl et al., 2019; Yang and Raine, 2009), others focused on a specific neurocognitive domain (e.g. executive function) but used heterogeneous tasks and conditions, some being unrelated to the investigated neurocognitive domain (e.g. reward and punishment tasks included in the executive domain) (Noordermeer et al., 2016). This heterogeneity limits the generalizability of results across different neurocognitive domains. Studying neural correlates of distinct and well-defined neurocognitive domains will result in a more precise understanding of the underlying neuropathological processes of CP/ASPD individuals. Moreover,

although Poeppl et al. (2019) performed a meta-analysis treating psychopathy as a unitary construct, it remains largely unknown whether their results are driven by factor 1 (i.e. affective/interpersonal facets) or factor 2 (i.e. impulsive/antisocial facets) of psychopathy (Latzman et al., 2019). Considering that a large number of psychometric tests includes antisocial behaviors (i.e. Factor 2), studying the specific correlates of brain functioning (i.e. callous-unemotional traits & severity of antisocial behaviors) is therefore crucial to better understand the heterogeneity in CP/ASPD individuals.

1.6. Aims of the current study

In all, the primary goal of this meta-analysis was to examine the neural processes of CP/ASPD individuals using only WB studies from five distinct neurocognitive domains based on the Research Domain Criteria (Cuthbert and Insel, 2013) and the classification made by Blair, Veroude et Buitelaar (Blair et al., 2018): Cognitive Control, Punishment and Reward Processing, Social Cognition and the Acute Threat Response. Main hypotheses are that CP/ASPD subjects would show a) reduced reactivity to threat (in comparison to HC), primarily in limbic and PFC regions, b) decreased activations in the inferior frontal gyrus/ventro-lateral PFC, insula, supplementary motor area during cognitive control tasks, c) deficits in regions implicated in self-reflection/consciousness such as posterior cingulate cortex/precuneus, medial PFC, the temporo-parietal junction as well as in limbic regions (i.e. amygdala, insula) during social cognitions tasks and d) deficit in valuation system, particularly in the striatum and the ventromedial PFC during reward processing and punishment processing. The current meta-analysis will thus shed light on task-domain dependent neural processing of CP/ASPD individuals. Establishing task-domain dependent neurocognitive deficits may enhance our capacity to target neurocognitive domains in early prevention to reduce the likelihood of problematic outcome associated with CP/ASPD. Additionally, a specific ROI-based meta-analysis on the amygdala was executed to better disentangle the role of this brain region in CP/ASPD subjects. Following current neurobiological models of CP/ASPD, a negative association between amygdala reactivity and callous-unemotional traits would be observed. Finally, meta-analytic evidence of relationships between brain responses and antisocial problems and CU traits was also executed based on dimensional studies.

2. Method

2.1. Selection procedures

2.1.1. Search strategies

A systematic search strategy, using three search engines (Google Scholar, PubMed and EMBASE), was performed independently by two researchers (MCA & JRD) up to February 2019 to identify relevant studies. The following search terms were used: ("*conduct problems*" or "*conduct disorder*" or "*disruptive behaviors*" or "*Antisocial personality disorder*" or "*psychopathy*" or "*sociopathy*" or "*dissocial personality disorder*") AND ("*functional magnetic resonance imaging*" ("*fMRI*")). Additional articles were searched by cross-referencing the reference lists of the included articles.

2.1.2. Selection criteria

Flow-chart and reasons of study exclusion can be retrieved in Supplementary Material. Articles were included if they met the following criteria: (1) original paper from a peer-reviewed journal, (2) inclusion of individuals with conduct/antisocial problems to disorder (CP/ASPD) without a comorbid major mental illness or organic impairment (i.e. forensic samples, schizophrenia) (3) use of functional magnetic resonance imaging; (4) use of a fMRI task related to a) cognitive control; b) social cognition (e.g. empathic decision-making, theory of mind); c) reward processing (e.g. monetary incentive delay task, passive avoidance tasks); d) punishment processing (e.g. monetary incentive delay task, Passive Avoidance tasks) or e) responses to threatening stimuli (e.g. negative images/faces); 5) description of results from group comparisons (CP/ASPD versus HC) and/or dimensional associations with antisocial problems and/or callous-unemotional traits; 6) use of WB methodology and/or amygdala predefined ROIs analyses. When studies reported only ROI analyses, authors were contacted to provide WB results (at $p < 0.001$ uncorrected threshold) (see Table 1 for authors that were contacted). The flow-chart and the reasons of studies' exclusion can be retrieved in Supplementary Material.

PRISMA guidelines were followed to achieve a high reporting standard (Moher et al., 2009) (Supplementary Material). Finally, we examined the moderation effect of CU traits. Since studies used different scales to measure CU traits, mean CU scores were converted using the well-established method *Percent of Maximum Possible scores* (POMP) that allows comparisons between different measures and populations (Cohen et al., 1999; Fischer and Milfont, 2010), as used in previous meta-analyses (Rogers and De Brito, 2016).

2.2. Coordinate-based meta-analysis

The current voxel-wise meta-analysis was performed using the Seed-based d Mapping with Permutation of Subject Images (SDM-PSI version 6.11) (Albajes-Eizagirre et al., 2019). Briefly, the SDM-PSI is a voxel-based meta-analysis software using peak coordinates and their t-values as reported from the original studies, to impute, for each study, multiple effect-size maps (Hedges' effect size) of contrast results (increased and decreased activations). Maps are then combined in a standard random-effects model considering sample size, intra-study variability and between-study heterogeneity (Radua et al., 2012a), and multiple imputations are pooled using Rubin's rules (Albajes-Eizagirre et al., 2019). The familywise error rate (FWER) of the results is calculated using a subject-based permutation test (Eklund et al., 2016). SDM-PSI uses MetaNSUE (Albajes-Eizagirre et al., 2018) to estimate the maximum likely effect size within the lower and upper bounds of possible effects sizes for each study separately and then adds realistic noise (Albajes-Eizagirre et al., 2019).

2.3. Meta-analysis procedure

To evaluate the strength of the evidence, a number of criteria were followed including the ten rules for neuroimaging meta-analyses (Müller et al., 2018). These criteria suggested that strong quality evidence would result from the included samples across the five neurocognitive domains (Supplementary Material).

First, whole-brain case-control main meta-analyses were performed to assess neural differences between CP/ASPD and HC on each neurocognitive domain. A binary covariate was included in the main analyses to adjust for studies having used a correction for multiple comparisons. Residual heterogeneity (I^2 statistic) of included studies was examined to assess robustness of results (I^2>50 % commonly indicates serious heterogeneity). Funnel plots were created to visually examine if findings had been driven by a small subset of studies or by studies with small sample sizes. Potential publication bias was assessed via a meta-regression of the effect size by its standard error (Egger et al., 1997; Sterne et al., 2011). We reported results using an uncorrected $p < 0.005$ threshold with a cluster extent = 10 voxels, since it was found to be optimally balance sensitivity and specificity (Lieberman and Cunningham, 2009; Radua et al., 2012a, b). as well as using FWER-corrected $p < 0.05$ with the threshold-free cluster enhancement approach (TFCE) and 5000 permutations (Smith and Nichols, 2009). Moreover, in order to assess the reliability of our results, we have performed several sub-analyses. In fact, meta-regression analyses were performed to assess the moderation effect of CU traits, age (i.e. potential changes from childhood to adulthood), percentage of participants from each sample that have received a comorbid Attention-Deficit/Hyperactivity Disorder

Table 1
Included samples and studies across meta-analyses on Case-Control studies (n = 65, k = 81).

First Author, Year	Case-Control Studies					
	Cognitive Control (k = 16)	Acute Threat Response (k = 26)	Reward Processing (k = 17)	Punishment Processing (k = 17)	Social Cognitions (k = 22)	Amyg. ROIs (k = 35)
Banich et al., 2007	X	–	–	–	–	–
Birbaumer et al., 2005*	–	–	–	X	–	X
Bjork et al., 2010	–	–	X	X	–	–
Bubenzer-Busch et al., 2016	–	X	X	X	–	–
Byrd et al., 2018 (A)	–	–	–	–	–	X
Byrd et al., 2018 (B)	–	–	–	–	–	X
Cardinale et al., 2018	–	–	–	–	X	–
Cohn et al., 2013 (A)	–	–	–	–	–	X
Cohn et al., 2013 (B)	–	–	–	–	–	X
Cohn et al., 2015 (A)	–	–	–	–	–	X
Cohn et al., 2015 (B)	–	–	–	–	–	X
Contreras-Rodríguez et al., 2013	–	X	–	–	–	–
Crowley et al., 2010	–	–	X	X	–	–
Decety et al., 2009	–	–	–	–	X	–
Deeley et al., 2006	–	X	–	–	–	–
Dong et al., 2017	–	–	–	–	X	–
Ewbank et al., 2018 (A)	–	X	–	–	–	X
Ewbank et al., 2018 (B)	–	X	–	–	–	X
Fairchild et al., 2014	–	X	–	–	–	X
Fanti et al., 2019 (A)	–	–	–	–	–	X
Fanti et al., 2019 (B)	–	–	–	–	–	X
Fehlbaum et al., 2018	X	–	–	–	–	–
Finger et al., 2012	–	–	X	X	–	–
Gatzke-Kopp et al., 2009	–	–	X	X	–	–
Geurts et al., 2016*	–	–	X	–	–	–
Gregory et al., 2015 (A)	–	–	X	X	–	–
Gregory et al., 2015 (B)	–	–	X	X	–	–
Herpertz et al., 2008	–	X	–	–	–	X
Hwang et al., 2016 (A)	X	X	–	–	–	X
Hwang et al., 2016 (B)	X	X	–	–	–	X
Hwang et al., 2018*	–	–	X	–	–	–
Jones et al., 2009	–	X	–	–	–	X
Kalnin et al., 2011	X	–	–	–	–	–
Klapwijk et al., 2016a	–	X	–	–	X	–
Klapwijk et al., 2016b	–	–	–	–	X	–
Kumari et al., 2009	–	X	–	–	–	–
Lockwood et al., 2013	–	–	–	–	X	–
Lozier et al., 2014 (A)	–	–	–	–	–	X
Lozier et al., 2014 (B)	–	–	–	–	–	X
Marsh et al., 2008	–	X	–	–	–	–
Marsh et al., 2011	X	–	–	–	X	X
Marsh et al., 2013	–	X	–	–	X	–
Meffert et al., 2013	–	–	–	–	X	–
Mier et al., 2014	–	–	–	–	X	X
O'Nions et al., 2014	–	–	–	–	X	–
Passamonti et al., 2010* (A)	–	X	–	–	–	X
Passamonti et al., 2010* (B)	–	X	–	–	–	X
Prehn et al., 2013a	–	X	–	–	–	X
Prehn et al., 2013b (A)	–	–	X	X	–	–
Prehn et al., 2013b (B)	–	–	X	X	–	–
Pujol et al., 2011	X	–	–	–	X	–
Rubia et al., 2008	X	–	–	–	–	–
Rubia et al., 2009a	X	–	–	–	–	–
Rubia et al., 2009b	–	–	X	X	–	–
Rubia et al., 2010	X	–	–	–	–	–
Sakai et al., 2017 (A)	–	–	–	–	X	–
Sakai et al., 2017 (B)	–	–	–	–	X	–
Schiffer et al., 2014	X	–	–	–	–	–
Schiffer et al., 2017	–	–	–	–	X	X
Schwenck et al., 2017	–	–	X	X	X	–
Sebastian et al., 2012	–	–	–	–	X	X
Sebastian et al., 2014 (A)	–	X	–	–	–	X
Sebastian et al., 2014 (B)	–	X	–	–	–	X
Sethi et al., 2018* (A)	–	X	–	–	X	–
Sethi et al., 2018* (B)	–	X	–	–	X	–
Thornton et al., 2017	X	X	–	–	–	X
van den Bos et al., 2014	–	–	–	–	X	–
van Lith et al., 2018 (A)	–	–	–	X	–	X
van Lith et al., 2018 (B)	–	–	–	X	–	X
Viding et al., 2012a (A)	–	X	–	–	–	X
Viding et al., 2012b (B)	–	X	–	–	–	X

(continued on next page)

Table 1 (*continued*)

First Author, Year	Case-Control Studies					
	Cognitive Control (k = 16)	Acute Threat Response (k = 26)	Reward Processing (k = 17)	Punishment Processing (k = 17)	Social Cognitions (k = 22)	Amyg. ROIs (k = 35)
Völlm et al., 2007	–	–	X	X	–	–
Völlm et al., 2010	X	–	X	–	–	–
White et al., 2012a	X	X	–	–	–	–
White et al., 2012b	X	X	–	–	–	–
White et al., 2013	–	–	X	X	–	–
White et al., 2014	–	–	X	X	–	–
White et al., 2015* (A)	–	–	–	–	X	X
White et al., 2015* (B)	–	–	–	–	X	X
White et al., 2018*	–	X	–	–	–	X
Zhang et al., 2015	X	–	–	–	–	–

Note. (A–B) refers to independent samples derived from the same studies; (1–2) refers to independent fMRI task derived from the same studies; Asterix (*) refer to authors that were contacted and provided results $p < 0.001$ uncorrected threshold.

(ADHD), percentage of participants being diagnosed with CD/ASPD diagnosis, percentage of participants from each sample that have received medication, repetition time of functional volumes and full width at half maximum of the smoothing kernel. For each subanalysis, alpha level was set at $\alpha = 0.005$ to reduce the risk of type 1 error associated with multiple testing.

For the amygdala ROI meta-analysis, we examined neural differences between CP/ASPD subjects and HC on left and right amygdala separately. ROIs were defined based on the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). Meta-analyses on dimensional associations between brain response (whole-brain and the amygdala ROIs) and antisocial problems and callous-unemotional traits, separately, were also performed to better understand the relationships between brain response and severity of antisocial problems/callous-unemotional traits.

3. Results

3.1. Characteristics of included studies for the whole-brain case-control meta-analyses

Sixty-one studies met the whole-brain inclusion criteria for the current meta-analysis. Of these studies, ten studies included two samples (Ewbank et al., 2018; Gregory et al., 2015; Hwang et al., 2016; Prehn et al., 2013b; Sakai et al., 2017; Sebastian et al., 2014; Sethi et al., 2018; van Lith et al., 2018; Viding et al., 2012b; White et al., 2015), resulting in a total of 71 samples. This represented a total of 1227 HC and 1328 CP/ASPD individuals (mean age = 20.15, range = 10.9–44.6 years old; 90 % males). CU traits were assessed for 54 samples with a mean POMP score of 58.95 % (range 22.9–84.4 %). We thus performed whole-brain case-control meta-analyses on studies based on five distinct neurocognitive domains: (A) Acute threat response (k = 26 samples of which a majority used tasks involving facial expressions of negative emotions); (B) Punishment Processing (k = 17 samples which included passive avoidance, MID or probabilistic response reversal tasks with monetary reward and loss); (C) Reward Processing (k = 17 samples, with most employing the same tasks as in punishment processing); (D) Social cognition (k = 22 samples with most using tasks involving evaluation of others' pain, ToM and empathic decision-making); (E) Cognitive Control (k = 16 samples, in which the majority used Stroop and Go-NoGo tasks). Only one contrast per fMRI task was selected to reduce bias associated with the inflation of study results. More detailed informations about the samples included and excluded as well as contrasts used are available in Supplementary Material. Also, interactive 3D models of our findings can be found at: github.com/JulDugre/3D_Neuroscience.

3.2. Whole brain case-control meta-analyses

3.2.1. Meta-analysis on Acute threat response

Twenty-six samples derived from 21 studies were included in the meta-analysis on acute threat response comprising a total of 450 HC and 517 CP/ASPD subjects (See Table 1). The mean age of CP/ASPD subjects was 17.95 (SD = 7.40), and 86 % of the total sample were males. Presence of medication was assessed for 19 samples with a mean percentage of 15.71 % for CP/ASPD subjects (ranging from 0 to 85.19 %). Presence of comorbid ADHD was assessed for 14 samples with a mean percentage of 50.83 %. Finally, percentage of samples diagnosed with a clinical diagnosis of CD/ASPD were provided for 15 samples which revealed that in average 81.1 % of individuals from these samples received a CD/ASPD diagnosis. In only 8 samples, all participants had received a clinical diagnosis of CD/ASPD.

During acute threat response tasks, CP/ASPD subjects showed no significant increased activations relative to HC. However, they revealed statistically significant decreased activations in the bilateral dorsal anterior cingulate gyrus, supplementary motor area (including median cingulate cortex), anterior insula (including the triangular part of the inferior frontal gyrus), bilateral middle occipital gyri, dorsolateral PFC, inferior parietal gyri and inferior temporal gyrus. (Table 3A; Fig. 1). These results did not survive the FWER correction ($p < 0.05$). Low between-study heterogeneity for each significant peak ($I^2 = 0.7$ %–17.64 %). Funnel plots suggested that none of the results were driven by small or noisy studies, and the test for potential publication bias was not statistically significant ($p = 0.665–0.717$).

CU traits were available for 22 samples (84.6 %) with a mean CU-POMP score of 61.64 % (range 22.9–78.1 %). However, no significant association with CU traits in CP/ASPD subjects was observed. Concerning percentage of samples under medication, we observed that the dorsal anterior cingulate cortex hypoactivity was negatively associated with medication level ($B = -0.011$, $p = 0.003$). Other subanalyses such as repetition time of functional volumes, full width at half maximum, age, comorbid ADHD and percentage of CD/ASPD diagnosis per sample were all statistically non-significant.

3.2.2. Punishment processing

Seventeen samples of individuals with CP/ASPD (from 14 studies) met the inclusion criteria for the meta-analysis on punishment processing (see Table 1). The meta-analysis comprised a total of 276 CP/ASPD subjects compared to 234 HC. The mean age of CP/ASPD subjects was 21.16 (SD = 9.95) and 95 % of the total sample were males. CU traits were available for 10 samples (58.8 %) with a mean CU-POMP score of 55.31 % (range 22.9–76.2 %). Sample's percentage under medication was assessed for 15 samples and suggest a mean percentage of 30.97 % (ranging from 0% to 100 %). ADHD diagnosis comorbidity was assessed for 10 samples, with a mean percentage of 46.2 % individuals with comorbid ADHD. Finally, percentage of participants from each sample that received a CD/ASPD was provided for 16 samples which revealed that in average 72 % of individuals from these samples received a CD/ASPD diagnosis. In only 5 samples, all participants had received a clinical diagnosis of CD/ASPD.

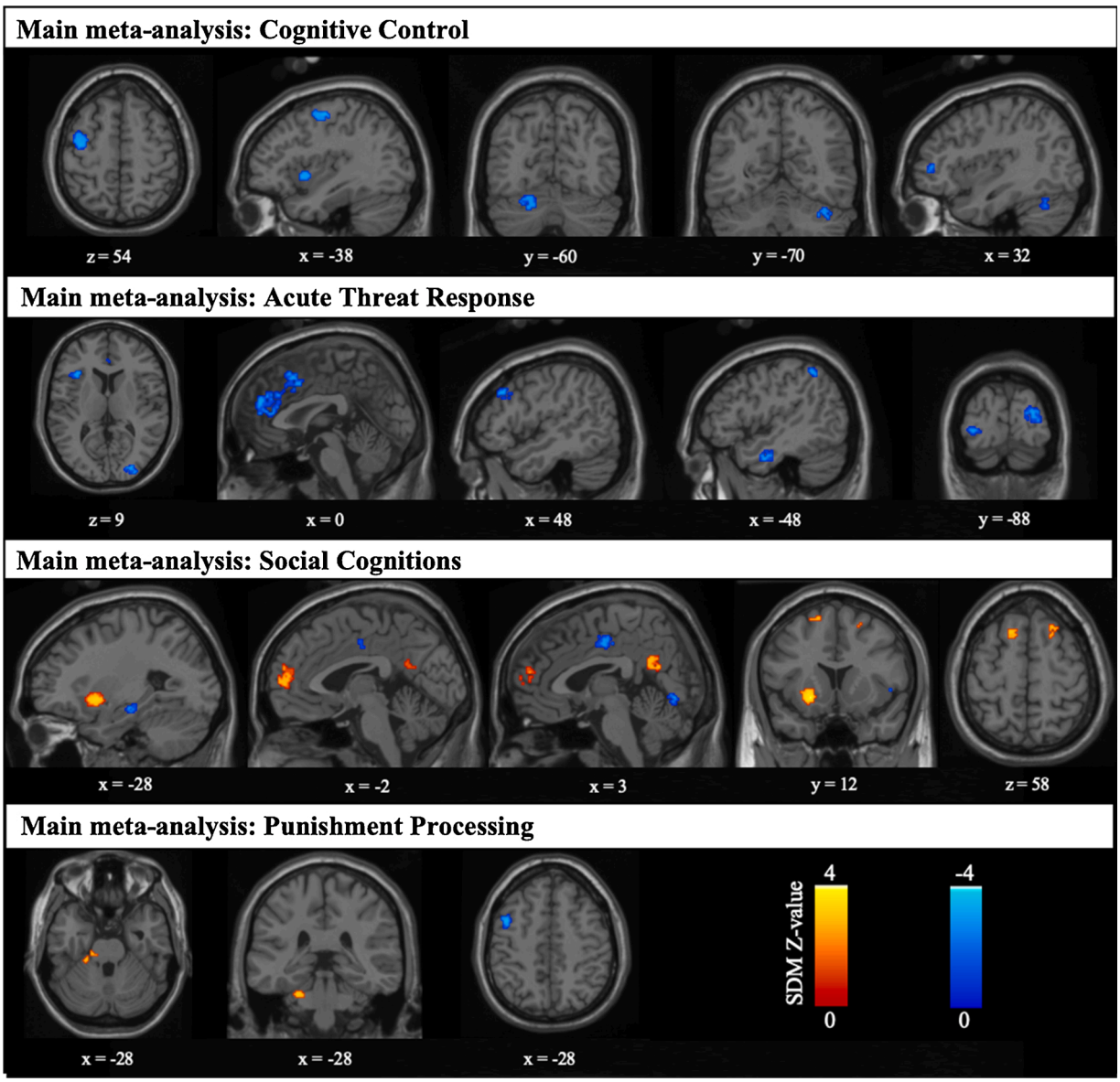

Fig. 1. Overlay of brain areas significantly impaired in CP/ASPD individuals compared to healthy subjects. These blobs were generated using the SDM p-value threshold of p = 0.005 uncorrected derived from the main analyses in Table 1. SDM = Seed-Based d Mapping.

Results revealed statistically significant increased activations in the left hemispheric Lobule IV (cerebellum) and the midbrain tegmentum in CP/ASPD subjects compared to HC. CP/ASPD subjects showed significant decreased activations in a cluster including the left premotor cortex BA6 (Table 3B; Fig. 1). These results did not survive the FWER correction ($p < 0.05$). Low between-study heterogeneity for each significant peak (I^2 = 1.94 % - 17.18 %). Funnel plots suggested that none of the results were driven by small or noisy studies, and the test for potential publication bias was not statistically significant (p = 0.862–0.976). Meta-regression analysis resulted in no significant association with CU traits in CP/ASPD subjects. Furthermore, no significant effect was observed between our results and moderators.

3.2.3. Reward processing

Seventeen samples from 15 studies met the inclusion criteria on reward processing (see Table 1) which comprised a total of 267 HC and 282 CP/ASPD subjects. The mean age of individuals with CP/ASPD was 22.93 years old (SD = 11.48) and 93 % were males. CU traits were available for only 8 samples (47.1 %) with a mean CU-POMP score of 50.4 % (range 22.9–74.4 %). Sample's percentage under medication was assessed for 14 samples and suggest a mean percentage of 27.17 % (ranging from 0% to 85.19 %). ADHD diagnosis comorbidity was assessed for 9 samples, with a mean percentage of 44 % across samples. Finally, percentage of samples diagnosed with a clinical diagnosis of CD/ASPD were provided for 16 samples which revealed that in average, 69 % of individuals from these samples received a CD/ASPD diagnosis. In only 6 samples, all participants had received a clinical diagnosis of CD/ASPD.

During reward processing fMRI tasks, CP/ASPD subjects showed no statistically significant differences in comparison to HC. Meta-regression analysis resulted in no significant association with CU traits in CP/ASPD subjects. Furthermore, no significant effect was observed between our results and moderators.

3.2.4. Social cognition domain

Twenty-two samples derived from 19 studies were included on social cognition comprising 461 CP/ASPD subjects compared to 419 HC. The mean age of CP/ASPD subjects was 19.86 years old (SD = 9.75) and 94 % of the total sample were males. Twenty samples provided CU traits (90.91 %) having a mean CU-POMP score of 57.25 % (range 28.8–84.4

%). Sample's percentage under medication was assessed for 17 samples and suggest a mean percentage of 15 % (ranging from 0% to 42.80 %). Comorbid ADHD diagnosis was assessed for 8 samples, with a mean percentage of 37 % individuals across these samples. Finally, percentage of samples diagnosed with a clinical diagnosis of CD/ASPD were provided for 11 samples which revealed that in average, 80 % of individuals from these samples received a CD/ASPD diagnosis. In only 5 samples, all participants had received a clinical diagnosis of CD/ASPD.

During Social Cognition tasks, CP/ASPD subjects showed statistically significant increased activations (as compared to HC) in the putamen, precuneus, medial PFC, bilateral dorsolateral PFC, fusiform gyrus, Crus I and Rolandic operculum. Furthermore, they showed reduced activations in the middle cingulate cortex, hippocampus, lingual and middle occipital gyri, inferior frontal gyrus and fusiform gyrus (Table 3D; Fig. 1). These results did not survive the FWER correction ($p < 0.05$). These peaks showed low between-study heterogeneity ($I^2 = 0.88$ %–13.6 %). Funnel plots suggested that none of the results were driven by small or noisy studies, and the test for potential publication bias was not statistically significant ($p = 0.674-0.830$). Meta-regression analysis resulted in no significant association with CU traits in CP/ASPD subjects. Furthermore, other subanalyses were all statistically non-significant.

3.2.5. Cognitive control domain

Sixteen samples from 15 studies met the inclusion criteria on cognitive control domain (See Table 1). These studies included a total of 320 individuals with CP/ASPD and 341 HC. The mean age of CP/ASPD subjects was 19.23 years old (SD = 9.97) and 84 % of these individuals were males. Ten out of 16 samples reported levels of CU traits (62.5 %), having a mean CU-POMP score of 58.1 % (range 24.96–78.13 %). Presence of medication was assessed for 14 samples with a mean percentage of 19.3 % for CP/ASPD subjects (ranging from 0 to 89.7 %). Presence of comorbid ADHD was assessed for 11 samples with a mean percentage of 35.9 % (ranging from 0 to 70.59). Finally, information about CD/ASPD clinical diagnosis were provided for 14 samples which revealed that in average 88 % of individuals received a CD/ASPD. In only 8 samples, all participants had received a clinical diagnosis of CD/ASPD.

During cognitive tasks, individuals with CP/ASPD showed no statistically significant increased activations in comparisons to HC. However, they showed decreased activations in several regions including the premotor cortex, anterior insula, middle temporal and middle frontal gyri as well as the hemispheric part of the Lobule VI and Crus I of the cerebellum (Table 3E; Fig. 1). These results did not survive the FWER correction ($p < 0.05$). These peaks showed low between-study heterogeneity ($I^2 = 1.67$ %–16.3 %). Funnel plots suggested that none of the results were driven by small or noisy studies, and the test for potential publication bias was not statistically significant ($p = 0.773-0.879$). Meta-regression analysis resulted in no significant association with CU traits in CP/ASPD subjects. Furthermore, no significant effect was observed between our results and moderators.

3.3. Meta-analysis based on amygdala region-of-Interest

Twenty-three studies that comprised 35 samples, were included in the amygdala ROI meta-analysis. More precisely, 503 healthy controls were compared to 701 CP/ASPD subjects. The mean age across CP/ASPD subjects was 17.72 (SD = 7.34) and the mean POMP score for CU was 60.93 % (k = 30). Presence of medication was assessed for 16 samples with a mean percentage of 18.5 % for CP/ASPD subjects (ranging from 0 to 100 %). Presence of comorbid ADHD was assessed for 18 samples with a mean percentage of 47.92 % (ranging from 15 % to 73 %). Finally, information about CD/ASPD clinical diagnosis were provided for 16 samples which revealed that in average 81 % of individuals received a CD/ASPD. In only 8 samples, all participants had received a clinical diagnosis of CD/ASPD.

No significant results were observed between CP/ASPD and HC subjects for both amygdala ROIs at a $p < 0.005$ uncorrected threshold. The left and right amygdala ROIs showed small to moderate between-study heterogeneity ($I^2 = 37.95$ & $I^2 = 27.43$, respectively). However, meta-regression across task-domains revealed a statistically significant negative relationship between CU traits and the right amygdala that survived a FWER correction for TFCE ($p < 0.05$) with 5000 permutations (i.e. x = 30, y=-2, z=-18; SDM-Z=-3.17, p = 0.005). This relationship was also observed when restricting studies to the acute threat detection domain (SDM-Z=-3.11, p = 0.0009) and social cognition domain (SDM-Z=-3.14, p = 0.0008) but not punishment processing. Moreover, the relationship between the right amygdala and CU traits across task domains remained significant when restricting to studies with children/adolescent (B = -1.87, $p < 0.001$). Although no significant relationship between the left amygdala and CU traits was observed across task domains, within-task domains subanalyses revealed significant negative association between the left amygdala and CU traits in the acute threat detection domains only (x=-24, y=-2, z=-14, SDM-Z=-2.70, p = 0.0035). No other significant effect was observed between the amygdala and moderators.

3.4. Meta-analyses based on dimensional associations between brain responses and severity of antisocial problems and callous-unemotional traits

3.4.1. Voxelwise relationship with antisocial problems

Ten samples from 9 studies were included in this meta-analysis (see Table 2). The relationship between brain response (at a whole-brain level) and severity of antisocial problems was assessed for 857 subjects from 6 samples related to the acute threat response domain, 3 to social cognitions, 1 to reward processing. The mean age was 25 years old (ranging from 10 to 39.8), with majority of samples being represented by adults (k = 6). Approximately 57 % of individuals in samples were males (ranging from 0 to 100%).

The main meta-analysis was performed across task domains due to the small sample size per task domains. Meta-analysis on dimensional studies assessing whole-brain correlates of antisocial problems revealed significant negative relationships with the anterior thalamic nuclei/mammillary body (x = 0, y=-10, z=-4; SDM-Z = -3.13; Cluster size = 39; p = 0.0008) and the right amygdala/parahippocampal gyrus (x = 24, y=-2, z=-28; SDM-Z = -3.01; Cluster size = 27; p = 0.0013). These results did not survive the FWER correction ($p < 0.05$). Main peaks showed low between-study heterogeneity ($I^2 = 1.91$–3.26). Funnel plots suggested that none of the results were driven by small or noisy studies, and the test for potential publication bias was not statistically significant ($p = 0.543-0.924$). Furthermore, the anterior thalamic nuclei (p = 0.001) and the right amygdala (p = 0.0007) remained statistically significant adjusting for CU traits. Due to the small sample size, no other subanalysis were performed.

3.4.2. Voxelwise relationship with callous-unemotional traits

Twelve samples from 11 studies were included in this meta-analysis (see Table 2). The relationship between brain response and severity of CU traits was assessed for 1009 subjects from 5 samples with fMRI task related to acute threat response domain, 2 to punishment processing, 1 to reward processing and 4 to social cognitions. The mean age was 24.75 years old (ranging from 10.05 to 39.8), with half of samples being represented by adults (k = 6). Approximately 69 % of individuals in samples were males (ranging from 0 to 100%).

The main meta-analysis was performed across task domains due to the small sample size per task domains. Meta-analysis on dimensional studies assessing voxelwise association with CU traits revealed significant negative association with the right superior temporal gyrus (x = 40, y = 8, z=-26, SDM-Z=-3.77, p = 0.00008). This peak did not survive the FWER correction ($p < 0.05$). The relationship between superior temporal gyrus and CU traits showed small between study heterogeneity ($I^2 = 4.94$ %), funnel plot suggest that this is not driven by small or noisy study and egger's test was statistically non-significant (p = 0.813). Due

Table 2
Included samples and studies across meta-analysis on dimensional studies (n = 40, k = 52).

First Author, Year	Dimensional Studies				Main Neurocognitive domain				
	Antisocial Behaviors		Callous-Unemotional						
	WB (k = 10)	Amyg. ROIs (k = 23)	WB (k = 12)	Amyg. ROIs (k = 31)	Cognitive Control	Acute Threat Response	Punishment Processing	Reward Processing	Social Cognitions
Byrd et al., 2018 (A)	–	X	–	X	–	–	X	–	–
Byrd et al., 2018 (B)									
Carré et al., 2013	–	X	–	X	–	X	–	–	–
Cohn et al., 2013 (A)	–	–	X	X	–	–	X	–	–
Cohn et al., 2013 (B)									
Cohn et al., 2015 (A)	–	–	–	X	–	–	X	–	–
Cohn et al., 2015 (B)									
Cohn et al., 2016 (A)	–	–	X	X	–	–	X	–	–
Cohn et al., 2016 (B)									
Contreras-Rodríguez et al., 2013	X	–	X	–	–	X	–	–	–
Cope et al., 2014	X	–	X	–	–	–	–	X	–
Decety et al., 2009	–	X	–	–	–	–	–	–	X
Decety et al., 2013a (1)	–	X	–	X	–	X	–	–	–
Decety et al., 2013a (2)	–	X	–	X	–	–	–	–	X
Decety et al., 2013b (1)	–	X	–	X	–	X	–	–	–
Decety et al., 2013b (2)	–	X	–	X	–	–	–	–	X
Decety et al., 2014	–	X	–	X	–	–	–	–	X
Dotterer et al., 2017	–	X	–	X	–	X	–	–	–
Ewbank et al., 2018 (A)	–	X	–	X	–	X	–	–	–
Ewbank et al., 2018 (B)									
Fairchild et al., 2014	X	X	–	–	–	X	–	–	–
Harenski et al., 2010	–	X	–	X	–	–	–	–	X
Harenski et al., 2014a	X	X	X	X	–	–	–	–	X
Harenski et al., 2014b	X	X	X	X	–	X	–	–	–
Hwang et al., 2016 (A)	–	–	–	X	–	X	–	–	–
Hwang et al., 2016 (B)									
Hwang et al., 2018*	–	–	–	X	–	–	–	X	–
Hyde et al., 2014	–	X	–	X	–	X	–	–	–
Hyde et al., 2016	–	X	–	X	–	X	–	–	–
Lozier et al., 2014 (A)	X	X	X	X	–	X	–	–	–
Lozier et al., 2014 (B)									
Marsh and Cardinale, 2014	–	X	–	X	–	–	–	–	X
Michalska et al., 2016	X	–	X	–	–	X	–	–	–
Passamonti et al., 2010* (A)	–	X	–	X	–	X	–	–	–
Passamonti et al., 2010* (B)									
Rilling et al., 2007	–	X	–	X	–	–	–	–	X
Sadeh et al., 2011a	X	X	X	X	–	X	–	–	–
Sakai et al., 2017 (A)	–	–	X	–	–	–	–	–	X
Sakai et al., 2017 (B)									
Schiffer et al., 2017	–	–	–	X	–	–	–	–	X
Schwenck et al., 2017	–	–	–	X	–	–	X	–	–
Sebastian et al., 2012	–	X	–	X	–	–	–	–	X
Sterzer et al., 2005	–	X	–	–	–	X	–	–	–
van Lith et al., 2018 (A)	–	–	–	X	–	–	X	–	–
van Lith et al., 2018 (B)							X		
Viding et al., 2012a (A)	–	–	–	X	–	X	–	–	–
Viding et al., 2012b (B)									
White et al., 2012b	–	–	–	X	–	X	–	–	–
White et al., 2015* (A)	–	–	–	X	–	–	–	–	X
White et al., 2015* (B)									
Yoder et al., 2015 (1)	X	–	X	–	–	–	–	–	X
Yoder et al., 2015 (2)	X	–	X	–	–	–	–	–	X

Note. (A–B) refers to independent samples derived from the same studies; (1–2) refers to independent fMRI task derived from the same studies; Asterix (*) refer to authors that were contacted and provided results $p < 0.001$ uncorrected threshold.

to the small sample size, no subanalysis were performed.

3.4.3. Relationship between Amygdala and antisocial problems

Twenty-three samples from 21 studies were included in this meta-analysis (see Table 2). Overall, the relationship between amygdala and severity of antisocial problems was assessed for 1807 subjects from 13 samples with a fMRI task related to the acute threat response domain, 1 to the punishment processing and 9 to social cognitions. The mean age was 21.18 years old (ranging from 10.8 to 44.6), with majority of samples being represented by adults (k = 13). Approximately 74 % of individuals in samples were males (ranging from 0 to 100%).

Main meta-analysis (across domains) and domain-specific meta-analyses (i.e. acute threat response and social cognitions) revealed no significant relationship between severity of antisocial behaviors and left/right amygdala reactivity. The left and right amygdala ROIs showed small to moderate between-study heterogeneity (I^2 = 30.15 & I^2 = 15.84, respectively). Subanalyses revealed no significant effects of moderators.

3.4.4. Relationship between the Amygdala and callous unemotional traits

Thirty-one samples from 29 studies were included in this meta-analysis (see Table 2). Overall, the relationship between the severity of CU traits and amygdala reactivity was assessed for 2264 subjects from 14 samples with a task related to the acute threat response domain, 6 to the punishment processing, 10 to social cognitions and 1 to reward processing. The mean age was 20.32 years old (ranging from 10.8 to 44.6), with majority of samples being represented by children/adolescent (k = 17). Approximately 79 % of individuals in samples were males (ranging from 0 to 100%).

Main meta-analysis (across domains) and domain-specific meta-analyses (i.e. acute threat response and social cognitions) revealed no significant associations between CU traits and amygdala reactivity. The left and right amygdala ROIs showed small between-study heterogeneity ($I^2 = 1.71$ & $I^2 = 2.77$, respectively). Subanalyses revealed no significant effects of moderators.

4. Discussion

The current study aimed to better identify the neural deficits of CP/ASPD subjects. First, in order to better describe brain differences between healthy subjects and CP/ASPD, we have performed coordinate-based case-control meta-analyses on whole brain studies according to five main neurocognitive pillars (i.e. acute threat response [k = 26, n = 517], reward processing [k = 17, n = 282], punishment processing[k = 17, n = 276], social cognitions [k = 22, n = 461] and cognitive control [k = 16, n = 320]) as well as a case-control meta-analysis on amygdala region-of-interest [k = 23, n = 701]. Second, to better describe the dimensional relationships between brain-behaviors underlying CP/ASPD subjects (i.e. Callous/unemotional traits/Factor 1 and antisocial problems/Factor 2), we have executed meta-analyses on dimensional studies assessing the relationship between whole-brain response and severity of antisocial problems (k = 10, n = 857) and severity of callous-unemotional traits (k = 12, n = 1009) as well as dimensional meta-analyses on amygdala region-of-interest and severity of antisocial problems (k = 23, n = 1807) and callous/unemotional traits (k = 31, n = 2264). To our knowledge, this is the largest study to date, and the first to investigate deficits in neural functioning of CP/ASPD subjects by considering these five neurocognitive domains. Our meta-analysis revealed that individuals on the *antisocial pathology* spectrum manifested significant neurofunctional deficits across four of the five domains when using a liberal statistical threshold (i.e. $p < 0.005$ uncorrected, minimal cluster size > 10 voxels), but none when using a conservative one (i.e. $p < 0.05$ FWE-corrected). That being said, the most prominent deficits observed were found in acute threat response, social cognitions and cognitive control, reflecting the importance of these neurocognitive domains as features of CP/ASPD individuals. We found no evidence of the moderation effect of CU traits on limbic system in response to threat, (Blair et al., 2014; Hyde et al., 2013; Viding et al., 2012a), and no significant differences between CP/ASPD and HC during reward processing were detected. However, we did observe limbic hypo-reactivity in response to threatening stimuli, hyper-reactivity of brain regions involved in self-other differentiation and hypo-activations during cognitive control tasks. Finally, contrarily to the widely held assumption in research on CP/ASPD subjects (Blair et al., 2014; Hyde et al., 2013; Viding et al., 2012a), we did not observe amygdala deficits in these individuals, though a negative relationship was observed with callous/unemotional traits (in the case-control ROI meta-analysis), and with severity of antisocial problems (in dimensional voxelwise meta-analysis).

During social cognition tasks, individuals with CP/ASPD exhibited important alterations in neural functioning in several regions such as the medial PFC and dorsolateral PFC, Precuneus, inferior frontal gyrus, middle cingulate cortex, hippocampus, insula and inferior frontal gyrus, putamen and cerebellar regions, which supports clinical observations suggesting significant socio-emotional impairments in CP/ASPD individuals (Chapman et al., 2018; Marsh and Blair, 2008; Oliver et al., 2011). Also, CU traits did not moderate these results. Deficits in several of these regions follow previous meta-analyses on regional grey matter volume in antisocial populations (putamen, insula, fusiform gyrus, medial PFC extending to the anterior and middle portion of the cingulate cortex) (Aoki et al., 2013; Rogers and De Brito, 2016) and overlap with brain regions underlying the neural model of morality and antisocial behaviors proposed by Raine & Yang (Raine and Yang, 2006). While the medial PFC, and precuneus are largely involved in processes implicated in self-reflection and theory of mind (Molenberghs et al., 2016; Schurz et al., 2014), the hippocampus and the dorsolateral PFC play a major role in episodic memory (i.e. autobiographical) (Spreng and Mar, 2012; Tulving and Markowitsch, 1998; Vargha-Khadem et al., 1997) and executive functions (Barbey et al., 2013), respectively. It is well known that CP/ASPD individuals show important deficits in social cognition, specifically regarding the recognition and representation of emotional states of others (Chapman et al., 2018; Marsh and Blair, 2008; Mellentin et al., 2015). As such, our results suggest that the impairments of CP/ASPD subjects regarding social cognition may arise from inefficient functioning of brain regions involved in the mediation between self/-other perspectives (i.e. medial PFC & Precuneus) and in emotional episodic memory (i.e. hippocampus). Although the putamen is frequently considered as a motor structure (Alexander et al., 1986), recent findings suggest that this region may also be involved in the interaction between memory, action and reward (Guo et al., 2018; Koster et al., 2015; Sadeh et al., 2011b). It can be argued that the alterations observed in the putamen underlie impairments in making prosocial decisions during social interactions (e.g. proneness to selfish/self-benefiting decisions at the cost of losses of others) in CD/ASPD individuals (Eimontaite et al., 2019; Schreuders et al., 2018). See Fig. 2 for functional characterization of our results, based on meta-analytical evidence.

During acute threat response tasks, CP/ASPD subjects manifested decreased activations in the anterior and middle cingulate cortex, anterior insula, and dorsolateral PFC. These brain regions are known to be largely implicated in emotional processing (Fan et al., 2011; Fusar--Poli et al., 2009; Kurth et al., 2010; Lamm et al., 2011). More specifically, whereas the dorsal portion of the anterior cingulate cortex and the dorsolateral PFC have been associated with learned emotional responses to threat stimuli and (re-)appraisal of threat (Etkin et al., 2015; Hartley and Phelps, 2010; Mechias et al., 2010), the insula is known to be involved in the integration of the interoceptive state, but also in predicting aversiveness of stimuli (Aupperle Robin and Martin, 2010) (See Fig. 2 for functional characterization of our results, based on meta-analytical evidence). The alterations observed in the anterior insula are consistent with results of previous (structural and functional) neuroimaging meta-analyses of people with disruptive behaviour disorders which all reported alterations in this brain region (Alegria et al., 2016; Aoki et al., 2013; Noordermeer et al., 2016; Poeppl et al., 2019; Rogers and De Brito, 2016). Contrarily to our observations, Poeppl et al.'s (2019) meta-analysis showed a hyperactivation of the anterior insula in psychopaths. However, this was mostly associated with functional characterization of cognitive rather than emotional subdomains. As such, these results suggest that the anterior insula alterations could be a potential neural marker of abnormal emotional processing in CP/ASPD individuals, specifically in response to acute threat stimuli. As previously suggested, individuals with high propensity for aggression (i.e. CP/ASPD subjects) are thought to exhibit increased acute threat responsiveness (Blair et al., 2018; Blair, 2016). Though, during acute threat response tasks, we observed no significant limbic hyperactivations in CP/ASPD individuals in comparison to HC. In fact, we rather observed significant hypoactivations in several regions that were not moderated by CU traits, contrasting with the dual pathway hypothesis (Blair et al., 2014; Hyde et al., 2013; Viding et al., 2012a). It is worth mentioning that no direct between-group difference in amygdala activation was detected in the current case-control fMRI meta-analyses,

Table 3
Results of the meta-analyses of whole-brain fMRI studies on neural correlates of the antisocial spectrum.

Contrast Results	L/ R	*MNI* Coordinates	*Z* value (a)	*P* Value (b)	No. of voxels (c)	Breakdown (No. of voxels) (c)
A. Acute Threat Response (k = 26)						
Healthy Controls > CP/ASPD						
dACC	R	8, 40, 20	−3.27	0.0005	277	R ACC (80); L mSFG (54); L ACC (108)
SMA	L	−4, 18, 46	−3.18	0.0007	136	L SMA (69); L MCC (21); R MCC (20)
MOG	R	24, −88, 10	−3.38	0.0003	120	R MOG (72); R SOG (20)
aInsula	L	−36, 22, 8	−3.28	0.0005	101	L Insula (60); L IFG triang (34)
ITG	L	−48, −10, −28	−3.12	0.0009	53	L ITG (46)
MOG	L	−32, −88, −2	−3.21	0.0006	40	L MOG (30)
dlPFC	R	48, 30, 34	−3.28	0.0005	36	R dlPFC (36)
IPG	L	−48, −50, 52	−3.06	0.0011	31	L IPG (31)
SMA	R	60, −46, 28	−2.96	0.0015	12	R SMA (12)
B. Punishment Processing (k = 17)						
CP/ASPD > Healthy Controls						
Lobule IV (Hemispheric)	L	−24, −34, −30	3.12	0.0009	31	Lobule IV (23)
Midbrain Tegmentum	L	−18, −28, −28	2.74	0.0031	11	Midbrain Tegmentum (11)
Healthy Controls > CP/ASPD						
Premotor Cortex (BA 6)	L	−44, 6, 46	−3.44	0.0002	54	Premotor Cortox (50)
C. Reward Processing (k = 17)						
No significant results	–	–	–	–	–	–
D. Social Cognition (k = 22)						
CP/ASPD > Healthy Controls						
Putamen	L	−22, 12, −8	3.93	0.00004	176	L Putamen (85); BA 48 (37)
Precuneus	R	4, −60, 20	2.95	0.0016	103	R Precuneus (49); L Precuneus (24)
mPFC	L	−2, 52, 8	2.82	0.0024	90	L mPFC (72)
dlPFC	L	−16, 14, 60	3.12	0.00091	61	L dlPFC (42); L SMA (11)
dlPFC	R	24, 22, 54	3.01	0.0013	56	R dlPFC (47)
FF Gyrus	R	28, −86, −8	2.93	0.0017	18	R Fusiform Gyrus (18)
Rolandic Operculum	R	42, −18, 16	2.75	0.0031	14	Rolandic Operculum (10)
Crus I	R	26, −68, −32	2.66	0.0039	13	Crus 1 (10)
Healthy Controls > CP/ASPD						
MCC	R	8, −16, 46	−2.93	0.0017	90	R MCC (65); L MCC (18)
Lingual Gyrus	R	6, −76, −12	−2.93	0.0017	34	R Lingual Gyrus (17)
Hippocampus	L	−28, −22, −16	−2.90	0.0019	32	L Hippocampus (25)
MOG	L	−42, −78, 4	−2.96	0.0015	20	L MOG (17)
IFG triang.	R	48, 20, 0	−2.8	0.0025	18	R IFG (10)
FF Gyrus	L	−42, −56, −20	−2.73	0.0032	12	L FF Gyrus (11)
E. Cognitive Control (k = 16)						
Healthy Controls > CP/ASPD						
Premotor cortex BA 6	L	−42, −4, 54	−3.31	0.00048	131	Premotor cortex BA 6 (131)
Lobule IV (Hemispheric)	L	−26, −72, −24	−2.85	0.0022	80	L Lobule VI (61); L Crus 1 (19)
aInsula	L	−38, 10, −4	−3.14	0.00084	40	L aInsula (37)
MTG	R	60, −14, −10	−2.91	0.0018	40	R MTG (31)
Crus 1	R	36, −60, −30	−2.84	0.0023	30	R Crus 1 (19); R Lobule VI (Hemisph.)(11)
vlPFC	R	38, 48, 0	−2.83	0.0023	27	R vlPFC (19)
SMG	L	−58, −40, 26	−2.79	0.0026	12	SMG (10)
Dimensional studies – Severity of Antisocial problems (k = 13)						
Negative Association						
aThal./Mamm.	–	0, −10, −4	−3.13	0.00089	39	Anterior thalamic nuclei; Mammillary Bodies (32)
Amyg./Parahipp.	R	24, −2, −28	−3.01	0.00131	27	Parahippocampal gyrus; Amygdala (19)
Dimensional studies – Severity of Callous-unemotional traits (k = 15)						
Negative Association						
Superior Temporal Gyrus	R	40, 10, −26	−3.77	0.00008	190	STG (117); MTG (62)

Note. k = number of samples; ; L = Left; R = Right; ACC = Anterior Cingulate Cortex; AG = Angular Gyrus; SFG = Superior Frontal Gyrus; mSFG = Medial Superior Frontal Gyrus; mPFC = Medial Prefrontal Cortex; SMG = Supramarginal Gyrus; IPL = Inferior Parietal Lobule; MOG = Middle Occipital Gyrus; SOG = Superior Occipital Gyrus; aInsula = Anterior Insula; pInsula = Posterior Insula; IFG Triang = Triangular part of the Inferior Frontal Gyrus; ITG = Inferior Temporal Gyrus; MTG = Middle Temporal Gyrus; SMA = Supplementary Motor Area; MCC = Median Cingulate Cortex; MFG = Middle Frontal Gyrus; IPG = Inferior Parietal Gyris; PreC = Precentral Gyrus; PCC = Posterior Cingulate Cortex; MCC = Median Cingulate Gyrus; Rolandic Operc = Rolandic Operculum; vlPFC = ventro-lateral PFC; LG = Lingual Gyrus; FF Gyrus = Fusiform Gyrus;aThal/Mamm. = anterior thalamic nuclei/Mammillary Bodies; Amyg./Parahipp. = Amygdala/Parahippocampal gyrus; STG = Superior Temporal Gyrus.
(a) Voxel probability threshold: p = 0.005 uncorrected; (c) Cluster extent threshold: 10 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.
*Remained statistically significant after correcting threshold (TFCE) of $p < 0.05$.

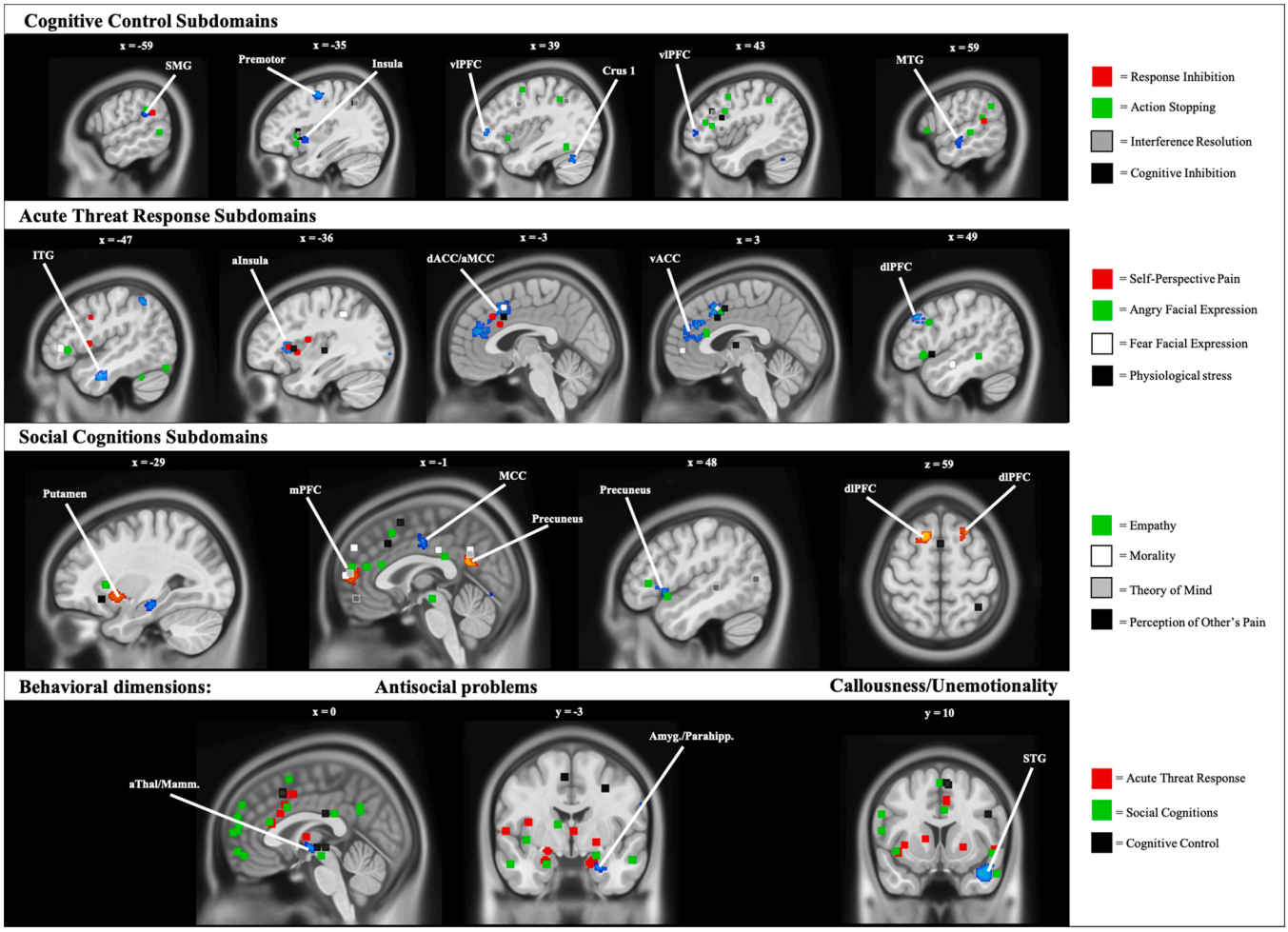

Fig. 2. Meta-analytical evidence of functional brain correlates of the antisocial spectrum with spatial functional characterization of the 3 main domains (i.e. Acute Threat Response, Social Cognition and Cognitive Control) and 12 subdomains based on nonexhaustive meta-analytical findings: **Cognitive Control Subdomains:** Response Inhibition (Red: Hung et al., 2018), Action Stopping (Green: Rae et al., 2014), Interference Resolution (Grey: Nee et al., 2007), Cognitive Control (Black: Hung et al., 2018); **Acute Threat Response Subdomains:** Self-perspective Pain (Red: Jauniaux et al., 2019), Angry Facial Expression (Green: Fusar-Poli et al., 2009), Fear Facial Expression (White: Fusar-Poli et al., 2009), Physiological Stress (Black, Kogler et al., 2015). **Social Cognitions Subdomains:** Empathy (Green: Bzdok et al., 2012), Morality (White: Bzdok et al., 2012); Theory of Mind (Grey: Bzdok et al., 2012), Perception of Other's Pain (Black: Jauniaux et al., 2019). **Antisocial problems and Callousness/unemotionality dimensions:** Acute Threat Response (Red), Social Cognition (Green), Cognitive Control (Black). SMG = Supramarginal Gyrus; vlPFC = Ventrolateral Prefrontal Cortex; MTG = Middle Temporal Gyrus; ITG = Inferior Temporal Gyrus; aInsula = Anterior Insula; dACC/aMCC = Dorsal Anterior Cingulate Cortex/Anterior Middle Cingulate Cortex; vACC = ventral ACC; dlPFC = Dorsolateral PFC; mPFC = median PFC; aThal/Mamm. = anterior thalamic nuclei/Mammillary Body; Amyg./Parahipp. = Amygdala/Parahippocampal gyrus; STG = Superior Temporal Gyrus.

although functional deficits were observed in a previous meta-analysis across neurocognitive domains in psychopathic individuals (Poeppl et al., 2019). Though, no amygdala abnormalities were observed in Alegria et al.'s (2016) meta-analysis on hot executive function and on emotional tasks. Likewise, discrepant results have been observed in structural imaging studies examining amygdala volumes in antisocial populations (Aoki et al., 2013; Noordermeer et al., 2016; Rogers and De Brito, 2016). Furthermore, in our ROI meta-analysis, CP/ASPD and HC did not statistically differ on amygdala reactivity. However, a meta-regression revealed significant negative associations between levels of callous-unemotional traits and the right amygdala activity. Albeit only observed in the ROI meta-analysis, this result is consistent with past theories indicating that the amygdala hypoactivity represents a biomarker of CU traits in children with CP (Blair et al., 2014; Hyde et al., 2013; Viding et al., 2012a).

The meta-analysis on cognitive control revealed that CP/ASPD subjects, in comparison to HC exhibited reduced activation in premotor cortex, anterior insula, ventrolateral PFC and cerebellar regions. These brain regions are key areas of cognitive control (Aron et al., 2014; Cai et al., 2014; Nee et al., 2007; Rae et al., 2014). In fact, it has been found that the right ventrolateral PFC plays a critical role in motor inhibition in healthy individuals, while the anterior insula is involved in the processing of the significance (i.e. motivational and affective) of inhibitory failure (Hester et al., 2004; Li et al., 2008; Padmala and Pessoa, 2010; Ramautar et al., 2006). Alegria et al.'s (2016) prior meta-analysis also observed reduced activation in the insula together with temporal and striatal regions. The findings furthermore resonate with previous structural meta-analyses on grey matter volume in CP/ASPD that showed volumetric deficits in the insula (Aoki et al., 2013; Noordermeer et al., 2016; Rogers and De Brito, 2016) and ventrolateral PFC (Noordermeer et al., 2016; Rogers and De Brito, 2016), which suggest potential neurobiological markers of cognitive control deficits. Importantly, considering that CP/ASPD subjects display more errors in prepotent response inhibition tasks (i.e. incongruent trials of the Stroop task and No-Go trials of the Stop-Signal task) (Chamberlain et al., 2016; Zeier et al., 2012), our results not only suggest that CP/ASPD individuals display deficits in motor inhibition (right ventrolateral PFC), but the inhibitory failures are also not processed as being affectively and motivationally significant (anterior insula), which results in difficulties in learning from response-inhibition mistakes.

Furthermore, it has been suggested that reinforcement-based decision-making (i.e. punishment and reward processing) is deficient in CP/ASPD subjects (Blair et al., 2018; Byrd et al., 2014). The meta-analysis on punishment processing tasks, revealed small but nevertheless significant differences. CP/ASPD subjects showed increased activations in the hemispheric lobule IV and midbrain tegmentum, and decreased activations in the premotor cortex BA6, in comparison to HC. However, it should be noted that previous meta-analyses on punishment processing in healthy subjects did not observe activation abnormalities in regions detected in our meta-analysis (Dugré et al., 2018; Knutson and Greer, 2008; Liu et al., 2011; Oldham et al., 2018). In view of the small number of studies on punishment processing, results should be interpreted cautiously. Nonetheless, there is a clear need for future studies on punishment processing in this specific population to support literature reviews suggesting punishment processing deficits in CP/ASPD subjects (Blair et al., 2018; Byrd et al., 2014). Regarding reward processing, we found no significant difference between CP/ASPD subjects. As indicated by a recent literature review on neuropsychological and fMRI studies, primary deficits in reward processing are inconclusive as studies have produced conflicting results (Byrd et al., 2014). Since it is largely known that dysfunction in reward processing is associated with substance misuse (Luijten et al., 2017), it is plausible that hyposensivity to reward characterize only particular subgroups of CP/ASPD individuals (i.e. those with a comorbid substance use problems). Future studies are thus needed to clarify the role of reward processing in CP/ASPD subjects.

Finally, through voxelwise meta-analyses on dimensional studies assessing brain- behaviour relationships, we observed that the amygdala was negatively associated with severity of antisocial behaviors but not severity of callous-unemotional traits. Furthermore, this relationship remained statistically significant adjusting for CU traits, suggesting that CU traits did not suppress the relationship between antisocial behaviors and the amygdala reactivity. The current neurobiological models of CP/ASPD posit that the amygdala hypo-reactivity is closely related to high callous-unemotional traits (Blair et al., 2014; Hyde et al., 2013; Viding et al., 2012a). Through a recent systematic review, some authors have suggested that the relationship between CU traits and emotional hypo-reactivity is more complex than previously thought, as some subjects with low CU may also show reduced emotional responsiveness (Northam and Dadds, 2020). That said, future studies should investigate the mediation effect of several factors that could alter the CU-amygdala reactivity including the attentional load, severity of antisocial behaviors, stimuli type (e.g. facial/non-facial stimuli), tasks instructions (e.g. implicit/explicit), the socio-emotional context (e.g. self/other tasks). However, it should be noted that in our meta-analysis on dimensional studies, the severity of antisocial problems was principally assessed by the Factor 2 – impulsivity/antisocial of psychometric scales measuring psychopathy (e.g. PCL-R). This could have led in inflating results from antisocial- yet psychopathic traits, rather than antisocial problems specifically.

The current meta-analysis showed that subjects on the antisocial spectrum had several neurofunctional deficits within four distinct neurocognitive domains. In fact, these findings provide critical insights on the neural functioning of antisocial subjects in different cognitive and emotional contexts. Moreover, our results were not influenced by CU traits, age and fMRI characteristics; no potential publication bias was observed. Notwithstanding the significant results of this meta-analysis, there are limitations that need to be acknowledged. First, the methodology used is based on peak coordinates and their effect size rather than raw statistical brain maps, thus reducing the results accuracy (Radua et al., 2012a). Second, we used an uncorrected threshold of $p < 0.005$. Although previous studies have shown that this threshold adequately controls the false positive rate (Radua et al., 2012a), it remains an approximation of corrected results. Following this, when using a more conservative statistical threshold ($p < 0.05$ FWE-corrected), the meta-analyses yielded no significant results. This could be due to several reasons: a) case-control studies generally included a small number of cases (mean size per study of 19 *versus* 101 in dimensional studies) and b) the heterogeneity that was not captured in this meta-analysis (e.g. subgroups), could have reduced our ability to observe results surviving conservative statistical thresholding. Although our liberal statistical threshold is generally used in fMRI literature (Lieberman et Cunningham, 2009) and in meta-analyses on neuroimaging studies (Radua et al., 2012a), we have reported results from both statistical thresholding to reduce the bias toward studying large rather than small effects in fMRI results and move beyond the *p-value* (Lieberman et Cunningham, 2009). The results reported in this meta-analysis are general trends from a heterogeneous population, therefore future studies should seek to replicate our results within well-defined homogeneous groups of antisocial subjects rather than developing theoretical framework solely based on p-value. Third, we included the whole spectrum of antisociality ranging from those with antisocial problems to those meeting the criteria for CD/ASPD. Since there are too few studies that included only participants meeting clinical diagnosis of CD/ASPD, it was not possible to examine directly the potential specific task-related neural functioning within those meeting clinical criteria of CD/ASPD only. We did nonetheless perform a subanalysis to investigate whether our results were associated with percentage of samples with CD/ASPD. Future studies should aim to include more systematically the percentage of their participants that meet clinical criteria of CD/ASPD. Fourth, it would have been optimal to examine the potential moderation effect of other important psychopathological factors such as substance use, psychiatric comorbidities (e.g. anxiety/depression), as well as specific subtypes of antisocial problems (e.g. aggression/rule-breaking behaviors, Tremblay, 2010 or reactive/proactive aggression, Raine et al., 2006). However, this was not feasible due to differences in psychometric scales across studies or due to the low quality of reporting of clinical data. Fifth, the number of samples in the reward and punishment processing meta-analyses was relatively small. Consequently, the results of these analyses should be interpreted with restraint. As anticipation and outcome of punishment processing are two distinct temporal phases with similar yet different networks (Dugré et al., 2018; Oldham et al., 2018), it was not possible to distinguish both phases in the present meta-analysis due to the small number of studies. Hence, more studies are necessary to test the hypothesis of deficits in encoding unexpected punishment and integrating cue-stimulus association in CP/ASPD individuals, with confidence (Blair et al., 2018; Byrd et al., 2014). Finally, while the use of a POMP score has permit us to study linear relationship between phenotypes (e.g. antisocial behaviors and CU traits) and neurobiological markers, it is worth noting that there may be discrepancies between psychometric scales made for clinical *versus* community sample. Next meta-analyses should be aware of this and seek to perform subanalyses on scale-specific POMP scores.

5. Conclusion

To our knowledge, this is the first and largest meta-analysis of fMRI studies on the neural processes of CP/ASPD individuals in clearly distinct neurocognitive domains. The meta-analysis shows that the most prominent deficits were observed during Acute threat response (e.g. dorsal portion of the anterior cingulate cortex, inferior parietal lobule, anterior insula and dorsolateral PFC) and Social cognition subdomains (e.g. Putamen, middle to posterior cingulate cortex/precuneus, medial PFC, hippocampus). Moreover, the present meta-analysis offers potential neural markers of CP/ASPD, which do not appear to be moderated by CU. Growing evidence shows large heterogeneity among CP/ASPD individuals (Fanti, 2018; Raine et al., 2006; Tremblay, 2010). Although emphasis has been placed on CU traits as being crucial for distinguishing between subgroups, the neural alterations in other subgroups of CP/ASPD such as those with aggressive *versus* non-aggressive rule breaking profiles (Tremblay, 2010), reactive *versus* proactive aggressive behaviour (Raine et al., 2006) or those with high levels of anxiety and depressive traits (Dugré et al., 2019; Fanti, 2018) remains understudied.

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Appendix A. Supplementary data

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